REMARKS

**Status of the Claims and
Request for Rejoinder of Dependent Method Claims**

Claims 20-24, 27-30, 33, and 49-61 are currently pending. Claims 1-19 were previously canceled and Applicants cancel claims 25-26, 31-32, and 34-48 herein. All of those claims are canceled without prejudice or disclaimer, and Applicants reserve the right in future to re-present the subject matter of those claims.

Next, Applicants amend a few of the withdrawn claims to place their grammar in active voice, remove redundant phrases, and to depend them from claim 49. As the withdrawn claims recite methods of making and using the elected thrombin preparation claims and as they all depend from claim 49, Applicants request their rejoinder upon allowance of the elected claims. *See* M.P.E.P. § 821.04

Applicants also re-phrase claim 58 slightly to recite "sugar alcohol" rather than "polyalcohol," merely for better consistency with original claim 8 and other parts of the specification.

Finally, Applicants add three new thrombin preparation claims 59-61. Those claims fall within elected group of claims, and are supported throughout the application. For example, claim 59 is supported, among other locations, at page 3, lines 12-14, and in Tables 4-5. Claims 60 and 61 are supported, among other locations, in original claims 15-17 and at page 1, first full paragraph. Hence, the new claims do not introduce new matter. Further, because the new claims depend from claim 49, which was previously presented, they do not raise new issues requiring a further search.

Applicants respectfully request the entry of these amendments.

All of the Pending Claims have Written Description Support

The Office first contends that claims 49-58 lack support under 35 U.S.C. § 112, first paragraph. (Office Action at pages 2-3.) Applicants traverse that rejection.

First of all, literal, word-for-word, support is not the standard under 35 U.S.C. § 112. *See* M.P.E.P. §§2163 and 2163.02. Instead, material may be supported inherently or implicitly, as well as by express language. For example, the support need not be found in the actual words of the application. A figure or table may provide the support as well. For example, in the case of *Koito Mfg. Co., Ltd. v. Turn Key Tech, LLC*, 72 U.S.P.Q.2d 1190, 1199 (Fed. Cir. 2004), a claim reciting a flow channel that was "significantly thicker and wider" than an adjacent channel was supported by a figure depicting the general differences in the size and thickness of the two channels.

In any event, Applicants previously provided detailed descriptions of the support for each of claims 49-58, including literal word-for-word support for several of the amendments, which the Office now appears to overlook. (See the Response filed May 16, 2005.) Applicants further describe the support for several of the prior claim amendments in detail in the sections that follow.

1. "At least 12 months" or "at least 24 months" in Claim 49

The Office specifically contends that there is no support for the phrases "at least 12 months" and "at least 24 months" in claim 49, and several dependent claims. Yet, the Office overlooks that nearly word-for-word support for the 12-month time period is provided at page 3, lines 7-8. There, the application explicitly states that the claimed

thrombin preparations are stable in the liquid state and have "***thrombin activity after 12 months or more [that] is still over 70-80% of the initial level.***" Certainly, "12 months or more" is synonymous with "at least 12 months."

Stability of "at least 12 months" and "at least 24 months" at 20-25 °C is also expressly and clearly depicted in Table 5 on page 15. That table presents a test of stability at that claimed temperature, for several compositions whose ingredients are described at page 11, Table 4. For instance, columns 8 and 9 depict actual stability test results of claimed formulas, using the claimed coagulation test methodology. For example, at 20-25 °C, the thrombin activity of a formula comprising p-aminobenzamidine thrombin inhibitor, measured using a coagulation test with fibrinogen as a substrate, is 100.9% at 12 months, and 90.1% at 24 months. (See page 15, column 8.) Hence, if the activity is still about 100% at 12 months and about 90% at 24 months, it is evidently at least 70-80% after 12 or 24 months.

2. "Measured by a coagulation test with a fibrinogen substrate" in Claim 49

The Office also contends that there is no support for the recitation of how the stability of the thrombin preparations was measured. Again, Applicants point out that literal, word-for-word support is not the standard of 35 U.S.C. § 112. *See* M.P.E.P. §§2163 and 2163.02. In any event, the application explicitly states at the bottom lines of page 11 that "***the stability of the formulations was tested by determining the thrombin activity in a coagulation test with fibrinogen as substrate***" and that the results are depicted in the Table 5 at pages 12-15. Indeed, the only difference between the claimed language and the recitation at page 11 is in the grammatical format.

Hence, even though literal support isn't necessary to satisfy 35 U.S.C. § 112, literal support is actually provided in this case.

3. "At least 70%, 80%, 90%" Recited in Claim 49 and Dependent Claims

The Office next contends that those percentages have no support in the application. Yet again, many of those percentage stabilities are supported in the application on a nearly word-for-word basis. Others are depicted very clearly in the actual results presented on page 15.

For example, the language of claims 49 and 50 is nearly identical to the recitation at page 3, lines 7-8. Those claims recite that the "thrombin activity" is "at least 70% [or 80%] of its initial level prior to storage." Page 3 of the application states "thrombin ***activity after 12 months or more is still over 70-80% of the initial level.***" One of ordinary skill would recognize that "over 70-80%" after 12 months and "at least 70%" or "at least 80%" after 12 months are essentially the same.

Even further, the application at page 6, lines 16-19, states that "[i]t is possible via the process of the invention to produce thrombin preparations which can be stored in the liquid . . . state for . . . years and whose activity does not fall below 70-80% in this period."

One of ordinary skill would also find actual results, according the claimed coagulation method, in the table at page 15, columns 8 and 9. There, the stability is 100.9% or 90.6% at 12 months and 90.1% or 82.4% at 24 months for two different claimed preparations. Those results also demonstrate that the claimed thrombin preparations may be "at least 70%" and "at least 80%" and even "at least 90%" active after 12 months or 24 months.

4. "a maximum of 2% (w/v) sugar alcohol" in Claim 58

Finally, the Office contends that the limitation in dependent claim 58 of "a maximum of 2% (w/v) sugar alcohol" is not supported, but acknowledges that Table 4 presents 2% or less of mannitol. (Office Action at page 3, lines 1-3.) However, one of ordinary skill in the art would understand that mannitol is a representative example of a "sugar alcohol," and thus provides support for the limitation as recited in claim 58. (See original claim 8, for example.) Moreover, original claims 2 and 8 recite the optional addition of a "sugar alcohol" to the claimed preparations. Hence, one of ordinary skill would recognize that the formulations with 0, 1, or 2% (w/v) mannitol presented at page 11 are meant only as examples of such preparations, and are not meant to limit the claims to any particular sugar alcohol.

Rejection of Claims 39-45 and 48 under 35 U.S.C. §102(b) is Moot

The Office contends that the abstracts of either Lorne et al. or Allary et al. anticipate claims 39-45 and 48. (Office Action at pages 3-4.) Those claims are now canceled, rendering this rejection moot.

All of the Claims are Nonobvious

Finally, Applicants traverse the Office's rejection of claims 49-58 as allegedly obvious over either Lorne et al. or Allary et al. taken with Hanada et al., Brezniak et al. and Altshuler. (Office Action at pages 5-7.) Applicants note that Lorne and Allary appear cumulative and present the same work by the same authors. Hence, those publications are discussed jointly below. Moreover, the complete articles, as well as

English-language translations, have previously been made of record. (See the Notice of References Cited and attachments; July 6, 2004.)

A *prima facie* case of obviousness must meet three requirements: (1) all of the claim limitations must be taught or suggested; (2) there must be an objective teaching in the prior art, and not in the applicant's disclosure, to combine or modify the art; and (3) the prior art must provide a reasonable expectation of success in performing that combination or modification. *See* M.P.E.P. §§ 2141-2143.

To find a motivation to combine references, the Office must locate an objective suggestion or desire in the cited references to perform the invention as it is claimed. *See, e.g., Winner Int'l Realty Corp. v. Wang*, 53 U.S.P.Q.2d 1580 (Fed. Cir. 2000). There is no motivation to combine unless the references illustrate that the combination is desirable, and not just technically feasible. *See Id. and see In re Gordon*, 733 F.2d 900, 902, 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984).

The combination of references cited here does not meet that standard. Instead, the combination of Lorne or Allary with Hanada, Brezniak, and Altshuler would teach away from Applicants' claims.

First, Lorne and Allary do not suggest thrombin preparations with the claimed properties and ingredients. Instead, those publications teach a method of extracting thrombin from an impure solution. While a thrombin inhibitor may be used at an intermediate stage of those protocols, the articles explain that it must be removed. For example, Lorne explains that "the thrombin obtained . . . must obligatorily be treated by a preliminary dialysis or ultrafiltration in 1 M NaCl to dissociate the complex formed with the elution agent (i.e. the inhibitor)." (Lorne at page 399, final full paragraph, referring to

the steps shown at Table 1, page 398, or see the translation at page 15, second full paragraph.) It is only after the removal of the elution agents and salts that the publications teach preparing a thrombin solution for practical use. (*Id.*)

Moreover, those publications provide no suggestion that an inhibitor could help thrombin remain active after long periods of storage at ambient temperature in the way that Applicants claim. (See claim 49.) In addition, the publications point out that benzamidine-based inhibitors do not work well in the extraction procedure, and that the extraction should be performed with NaCl or arginine methylester elution agents instead. (Allary at page 135, or see the translation at page 10; Lorne at page 400, or see the translation at page 16, second and third paragraphs; see claims 55-56.) Hence, as a whole, Lorne and Allary teach away from preparing thrombin solutions having long term stability using a thrombin inhibitor as a stabilizer.

None of the other cited publications bridges that large gap in Lorne and Allary's teachings. Hanada also teaches away from the instant claims. It too uses a thrombin inhibitor only at an intermediate treatment stage during a process of purifying thrombin. It also teaches that all traces of the inhibitor should be removed. (*See* Hanada at col. 4, lines 13-28, and col. 5, Example 1.) Hanada, like Lorne and Allary, teaches that thrombin preparations should be protected and stored by lyophilization in pure form, in the absence of any thrombin inhibitors or other chemical additives beyond simple buffer ingredients. (*See* col. 5, lines 45-50.) In fact, the Office has previously recognized that Hanada teaches away from Applicants' invention in withdrawing earlier rejections over that publication. (Compare Examiner's Answer of July 29, 2004, to Office Action of November 28, 2003.)

Brezniak and Altshuler cannot fill the gap left by Lorne, Allary, and Hanada because they do not mention thrombin inhibitors whatsoever. In addition, Altshuler's solutions contain high concentrations of PEG or glycerol which increase the viscosity of the preparation. (Compare to dependent claim 59.) Hence, one of ordinary skill in the art reading all of these publications would not desire to make a thrombin preparation for practical room-temperature storage and use that includes a thrombin inhibitor. Instead, taken together, the publications suggest that an inhibitor should not be used. The courts have long explained that such teaching away is "strong evidence of unobviousness." *In re Hedges*, 783 F.2d 1038, 1041, 228 U.S.P.Q. 685, 687 (Fed. Cir. 1986).

For all of the reasons above, Applicants request the withdrawal of this rejection.

CONCLUSION

In light of these remarks, Applicants respectfully request the allowance of claims 49-60, and the rejoinder of amended, withdrawn claims 20-24, 27-30, and 33 which depend from claim 49.

This amendment is accompanied by a request for a one-month extension of time and fee payment. Please grant any extensions of time necessary to enter this amendment. If there is any fee due that is not otherwise found herewith, please charge the fee to Deposit Account No. 06-0916.

Respectfully submitted,

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